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Controlled Microwave-Assisted Synthesis of Fluoroquinolones

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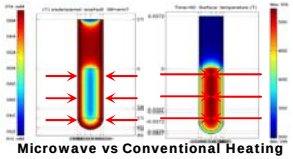
Introduction

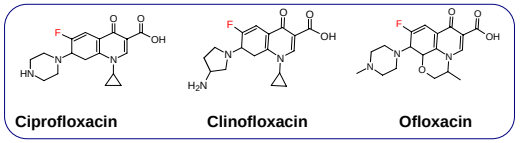
The emergence and alarming spread of bacterial, parasitical and viral strains that are resistant to clinically used drugs is the driving force behind the ongoing search of new antibacterial and antiviral drugs. The conventional methods of synthesis and isolation of anti-infective agents generally take weeks. The long time required for the multi-step synthesis of these agents makes the discovery process of new targets extremely cumbersome.
In recent years microwave irradiation has become very popular in shortening the time required for C-C and C-X formation from weeks to minutes due to its rapid transfer of energy.

The wall affects generally seen in conventional heating methods is completely eliminated in microwave assisted synthesis. MAOS not only are much faster, but also result in higher percent yield and purity of the final product (Pic. 1)



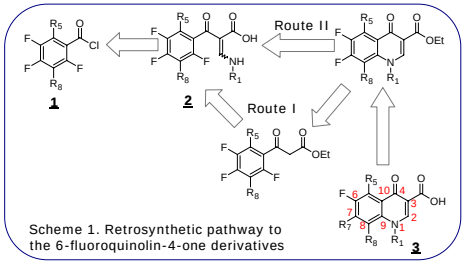
Microwave vs Conventional Heating

We have used MAOS for the synthesis of fluoroquinolones (generic structure in scheme 1, compound 3). These compounds are particularly interesting because of their board spectrum of activity against various bacteria, mycobacteria, and parasites. The majority of the clinical used fluoroquinolones have a fluoro group attached the 6-position, such as commercially available ciprofloxacin, norfloxacin and orfloxacin.



Ciprofloxacin Clinofloxacin Ofloxacin

The retrosynthetic scheme to obtain the targeted 6-fluoroquinoloes starting from commercially available acid chloride (1) is shown in scheme 1. The targeted quinolone is prepared through an intermolecular cyclization of enaminone intermediate (2) prepared using an (N-alkyl) acrylate (route II), this reported method is a milder condition and more efficient than the one depicted in the alternatives route I.



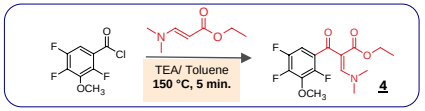
Scheme 1. Retrosynthetic pathway to the 6-fluoroquinolin-4-one derivatives

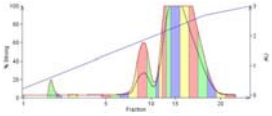
The literature published the procedures for synthesis of fluoroquinoline requires over one week time with a 15-18% overall yield. Single-mod controlled microwave synthesizer and capped vials were used in this multi steps synthesis. Optimization of the microwave synthesis was performed in Biotage Liberator (sealed vessels) with possibilities for automated dispensing of reaction components and automated vessel transfer. The conditions obtained from the small-scale runs (2-5 ml Vials) were directly applied to 20 mL vials for larger scale runs.

Controlled, single-mode microwave synthesizers and vials

Liberator Initiator 2-5 mL, 10-20 mL Vials

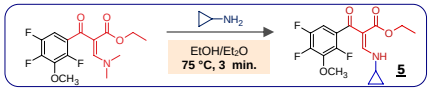
The targeted 6-fluoroquinoloe was prepared in five steps with a 65-70% overall yield. Starting from the reaction of commercially available acid chloride with ethyl 3-dimethylamino- arcylate, thus affording the *N*,*N* -dimethylnaminone intermediate 4. This reaction was carried out at 150 °C for 5 minutes[1]. The pure product was isolated using flash chromatography using Biotage SNAP cartridge with a 84% yield.



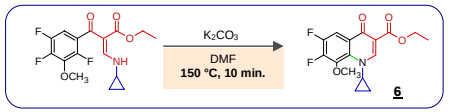


Solvent	n-Hexane, Ethyl acetate
Cartridge	SNAP silica, 50g
Flow rate	40 ml/min
Wavelength	Collection 254 nm

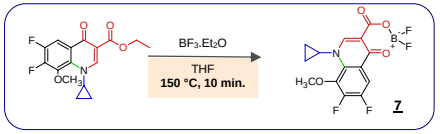
The *N*,*N* -dimethylnaminone intermediate 2 was reacted with cyclopropylamine to produce the enamine 4 in three minutes at 75 °C [2]. This amine exchange reaction is usually done at room temperature and takes over 3 hours. The enamine 5 was used in the next step without any purification at 98.6% purity.



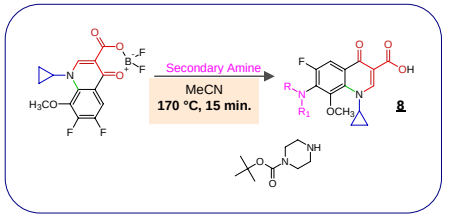
The enamine 5 was readily cyclized at 150 °C in 10 minutes using K_2CO_3 as base to yield the trifluoro ester 6 with an 85% yield[3]. The mild K_2CO_3 base was preferred to the most frequently used NaH, which in microwave assisted synthesis led to many by-products. This conventional cyclization reaction generally takes five hours at 100°C.



The introduction of the R_7 substituent through an aromatic nucleophilic substitution of the C-7 fluorine atom onto compound 6 was achieved in good yield under microwave irradiation when this position was activated as boron difluoride derivatives. The boron trifluoride etherate 7 was prepared under microwave irradiation at 150 °C in 10 minutes [4], with an 85% yield.



The literature reported aromatic nucleophilic substitution at C-7 is a time-consuming seven days process [5]. Using microwave irradiation this step was completed in 15 minutes at 170 °C [5].



Conventional synthesis requires 338 hrs.
Microwave assisted synthesis requires >1 hr.

In conclusion

We have developed a fast and general synthesis of 8-methoxy-substituted fluoroquinolone antibacterial agents by amination of 7-halo-6-fluoroquinolone-3-carboxylic acids in excellent yields, under microwave conditions.
We are confident this methodology will allow for the development of chemical libraries of fluoroquinolone analogues at the fraction of the normal cost and time for biological testing. Microwave heating did shorten the time required for multi steps synthesis fro week to less than one hour.

1: To a solution of triethylamine (20 mmol, 2.8 mL) and ethyl 3-dimethylamino-arcylate (12 mmol, 1.75 mL) in 7 mL of toluene was added dropwise a solution of 2,4,5-trifluoro-3-methoxybenzoyl chloride (10 mmol, 1.5 mL) in 7 mL of toluene. The reaction mixture was stirred at 150 °C for 5 min. The pure product was isolated using flash chromatography using Biotage SNAP cartridge

2: Compound 4 (785 mg, 2.37 mmol) in 1:2 EtOH/Et_2O (20 mL) was added to (0.38 mL, 5.48 mmol). After 3 minutes at 75 °C, The reaction mixture was evaporated under reduced pressure to result the pure product 5 at 86% yield.

3: Compound 5 (200 mg, 0.5 mmol) was dissolved in 5mL DMF and K_2CO_3 (220 mg,) was added. Reaction mixture was stirred for 10 min. at 150°C. filtered and 1 ml water was added to the solution then left in refrigerator for 30 min. white needle like precipitate was collated under vacuum filtration. 160 mg, 85.1%TLC: MeOH:DCM 1:9

4: $BF_3.Et_2O$ (MW. 141.93, d. 1.13, 0.75 ml, 5.9 mmol) was added to 4 (180 mg, 0.56 mmol) in suspension in THF (bp 65-67 °C) (10 mL) heated at 150 °C for 10 min., the clear reaction mixture was evaporated under reduced pressure. The crude oily residue was successively washed with Et_2O and water affording 5 as white solid 88%.

6: A solution of 1-(Diphenylmethyl)piperazine(252.35, 0.3 mmol, 76 mg) and 75 (69 mg, 0.2 mmol) in CH_3CN (bp 81-82) (4 mL) was heated in a microwave for 15 min. at 170 °C. After evaporation under reduced pressure, a yellow oil was collected.

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